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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/509,145	BERLIN, KURT	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-26 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 27 September 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-26 have been examined herein.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of amplifying a nucleic acid via rolling circle amplification wherein the 5' cytosine methylation status of the CG dinucleotides in the template strand are copied to the CG dinucleotides of the synthesized strand as recited in steps a-e of Claim 1, does not reasonably provide enablement for any amplification method wherein the 5' cytosine methylation status of the CG dinucleotides in the template strand are copied to the CG dinucleotides of the synthesized strand as recited in steps a-e of Claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the

predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn broadly to a method for amplifying a nucleic acid wherein the 5' cytosine methylation status of the CG dinucleotides in the template strand are copied to the CG dinucleotides of the synthesized strand. The method of amplification can be selected from ligase chain reaction, polymerase chain reaction, or rolling circle reaction. The claims are further limited by the recitation that the methylation is carried out by enzymatic means wherein said enzyme is maintenance methyltransferase such as DNA (cytosine-5) Methyltransferase (DNMT1). Additionally the claims state that the methyl group is obtained from the donor molecule S-adenosylmethionine.

Nature of the Invention

The claims are drawn broadly to a method for amplifying a nucleic acid wherein the 5' cytosine methylation status of the CG dinucleotides in the template strand are copied to the CG dinucleotides of the synthesized strand. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification at page 6 teaches that the methyl transfer reaction proceeds through a non specific binding of the transferase to the hemimethylated DNA strand,

identification of the target base followed by the recruitment of the methyl donor group, most commonly S-adenosyl-L-methionine (AdoMet) to the active site. DNA methyltransferases (m5C Mtase) attach a methyl group to the 5 position carbon. The reaction is carried out via a covalent intermediate between the enzyme and the base whereby the target cytosine is flipped through 180 degrees. The specification at page 7 further teaches that several species of methyltransferases have been identified, of particular interest to this invention are the family of maintenance methyltransferases that propagate the methylation pattern of hemimethylated DNA within the unmethylated strand, such as Dnmt1. In the past the epigenetic information carried by 5-methylcytosine was completely lost during PCR amplification. As a result the applicants have developed a new method for analyzing methylation patterns in which the epigenetic information carried by 5-methylcytosine is retained during PCR amplification.

The specification also teaches at pages 15-17 that the amplification methods can be selected from ligase chain reaction, polymerase chain reaction, or rolling circle replication. In the ligase chain reaction two probe oligonucleotides are hybridized to a single stranded template nucleic acid such that the 5' end of one oligonucleotide probe hybridizes next to the 3' end of the other oligonucleotide probe thereby allowing the two oligonucleotides to be joined together by a ligase. In the PCR reaction first the DNA double helix is denatured by transient heating. This is followed by the annealing of two species of primers, one to each strand of DNA. Subsequently the annealed primers are extended using a polymerase dNTPs. Both PCR and LCR require a denaturation step. The nucleic acid strands are heat denatured at approximately 95 °C thereby allowing

the resultant single stranded nucleic acid to be used as a template nucleic acid in subsequent cycles of amplification. In rolling circle replication the target nucleic acid becomes circularized. The circularized nucleic acid is then isothermally replicated (usually at about 30°C) using rolling circle replication primers and a polymerase enzyme.

The post filing date art of New England Biolabs teach that human DNA methyltransferase (Dnmt1) methylates cytosine residues in hemimethylated DNA at 5'....CG....3'. They also teach that the enzyme becomes inactive when heated at 65 °C for 20 min. Additionally S-adenosylmethionine (SAM) is used with Dnmt1 because it provides the methyl donor group. SAM must be stored at –20 °C and becomes inactive at 37°C.

Accordingly the specification, while being enabling for a method of amplifying a nucleic acid via rolling circle amplification wherein the 5' cytosine methylation status of the CG dinucleotides in the template strand are copied to the CG dinucleotides of the synthesized strand, does not reasonably provide enablement for any amplfiication method wherein the 5' cytosine methylation status of the CG dinucleotides in the template strand are copied to the CG dinucleotides of the synthesized strand because the methylation enzyme used (Dnmt1) is not heat stable and would therefore be inactivated during the denaturation step of PCR or LCR.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

It is unpredictable as to whether an amplification composition comprising Dnmt1 and S-adenosylmethionine could be used in a method to amplify nucleic acid via PCR

or LCR wherein the 5' cytosine methylation status of the CG dinucleotides in the template strand are copied to the CG dinucleotides of the synthesized strand. It is well known in the art that both PCR and LCR are performed at high temperatures. In fact the specification at page 29 teaches that denaturation step is carried out at 95 °C for 15 min. This is followed by the primer annealing step which is carried out at 55 °C for 45 seconds and then elongation step is done at 72 °C for 1.5 minutes. It is also known in the art that Dnmt1 becomes inactive when heated at 65 °C for 20 min. Additionally S-adenosylmethionine (SAM) becomes inactive at 37°C. Therefore it is unpredictable if Dnmt1 would lose its ability to methylate the synthesized strand after being exposed to reaction temperatures that are greater than 65°C. It is also unpredictable if SAM would lose its ability to donate a methyl group after being exposed to reaction temperatures greater than 37 °C.

Amount of Direction or Guidance Provided by the Specification:

The specification teaches methods for amplifying a nucleic acid via PCR, LCR and rolling circle amplification wherein the 5' cytosine methylation status of the CG dinucleotides in the template strand are copied to the CG dinucleotides of the synthesized strand. However there are no teachings in the specification that explain how Dmnt1 and SAM can be used in the methods of PCR or LCR since both Dmnt1 and SAM are not heat stable.

Working Examples:

Again, the specification teaches methods for amplifying a nucleic acid via PCR, LCR and rolling circle amplification wherein the 5' cytosine methylation status of the CG

dinucleotides in the template strand are copied to the CG dinucleotides of the synthesized strand. Example 1 in the specification is a method that for methylation retaining PCR amplification. However there is no data provided in the specification in shows this has actually been done successfully.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification does not teach how to amplify a nucleic acid via any amplifiction method wherein the 5' cytosine methylation status of the CG dinucleotides in the template strand are copied to the CG dinucleotides of the synthesized strand. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and

the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-25 are indefinite over the recitation of the phrase "methylation patterns of said genomic nucleic acids are maintained". This phrase in considered unclear because how the methylation patterns are maintained is not clearly defined in the claim. Additionally the claims are indefinite over the recitation of "said amplified nucleic acid" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 2 is indefinite over the recitation of the phrase "and all possible combinations thereof". Since the claim does not clearly define what constitutes "all possible combinations" one cannot determine the meets and bounds of the claimed subject matter.

Claim 4 is indefinite over the recitation of "the double stranded nucleic acids". There is insufficient antecedent basis for this limitation in the claim.

Claim 7 is indefinite over the recitation of "said enzyme". There is insufficient antecedent basis for this limitation in the claim.

Claim 9 is indefinite over the recitations of "the methyl group" and "the donor molecule S-adenosylmethionine". There is insufficient antecedent basis for these limitations in the claim.

Claim 21 is indefinite over the recitation of "the nucleic acid". There is insufficient antecedent basis for this limitation in the claim. It is unclear if "the nucleic acid" refers to the target nucleic acid or the amplified nucleic acid.

Claim 23 is indefinite over the recitation of "the methyl group carries a detectable label". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 11-13, 18-20 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Olek (US Patent 6214556 Issued 2001)

Regarding Claim 1 Olek et al teach a method comprising (i) obtaining a genomic DNA sample and treating the sample with a bisulfite solution, (ii) amplifying the treated sample, (iii) and detecting methylation using a mass spectrometer (Abstract and Column 22). In the instant case the bisulfite treatment followed by amplification is being interpreted as "an amplification method in which the methylation patterns of said genomic nucleic acids are maintained in the amplificate nucleic acid" because even

though the methylated cytosines are not present on the newly synthesizes strand, the pattern of where the methylated cytosines were present on the template strand can still be determined. Thus the methylation pattern is maintained.

Regarding Claim 2 Olek et al teach that the genomic DNA is obtained from cells or cellular components that contain DNA. Specifically Olek et al teaches that the genomic DNA was obtained from a tissue sample (Abstract).

Regarding Claims 11 and 12 Olek teaches that the extracted DNA can now be subjected to bisulfite treatment in untreated form, to shearing, or specific cleavage with restriction endonucleases (Column 11)

Regarding Claim 13 Olek et al teach a method wherein the detection step is carried out by means of time-of-flight MALDI spectrometry (Column 22).

Regarding Claim 18 Olek et al teaches a method wherein the primer oligonucleotides do not contain CG dinucleotides. Specifically Olek used two or more different oligonucleotides in each amplification, which oligonucleotides can be subdivided into two classes. These classes are characterized in that in one, the base guanine, and in the other, the base cytosine, is not represented, or hardly represented, or only represented in a 5' region (Column 15).

Regarding Claim 19 Olek et al teach a method wherein said amplificates are immobilized upon a solid phase (Column 17).

Regarding Claims 20 Olek et al teach a method wherein the amplificates comprise at least one chemical modification (Column 22).

Regarding Claim 25 Olek et teach a method which can be used to analyze methylation patterns in genomic DNA (Abstract).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 14-17 and 23-24 are rejected under 35 U.S.C. 103(a) as being obvious over Olek (US Patent 6214556 Issued 2001) in view of Monforte (US Patent 5965363 Issued 1999).

The teachings of Olek et al are presented above in paragraph 4.

Regarding Claim 14, Olek et al does not teach a method wherein the step of performing mass spectrometry on the nucleic acid sample also comprises a step of internal or external calibration.

However Monforte et al teach a method wherein the step of performing mass spectrometry on the nucleic acid sample also comprises a step of calibrating the mass spectrometer using internal calibrants (Column 20).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Olek et al by using internal calibrants for calibrating the mass spectrometer as suggested by Monforte in order to provide improved mass accuracy.

Regarding Claim 15 Olek et al does not teach prior to the detection step the nucleic acids are purified.

However Monforte et al teach method for isolating target nucleic acids from a multiplicity of impurities including undesirable nucleic acid fragments (including the complementary strand and flanking regions), proteins, salts, that would result in a poor quality mass spectrum (Column 14).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Olek et al by purifying the nucleic acid sample prior to detection as suggested by Monforte because the presence of impurities, especially salts, greatly affects the resolution, accuracy and intensity of the mass spectrometric signal. Contaminating primers, residual sample genomic DNA, and proteins, all can affect the quality of the mass spectra (Column 14).

Regarding Claim 16 Olek et al does not teach a method wherein the sample nucleic acids are single stranded.

However Monforte et al teach a method wherein the analysis of single-stranded amplified target nucleic acids is generally preferable since it provides a complete set of data with the minimal number of fragments and therefore simplifies the spectra and

facilitates an increase in the total number of target nucleic acids that can be analyzed in a single assay (Column 14).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Olek et al by using a single stranded nucleic acid sample as suggested by Monforte et al in order to simplify the spectra and facilitate an increase in the total number of target nucleic acids that can be analyzed in a single assay (Column 14).

Regarding Claim 17 Olek et al do not teach a method wherein the amplificate nucleic acids are less than 100 base pairs in length.

However Monforte et al teach that the amplified nucleic acids are typically less than 100 bases in length (Column 11).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Olek et al by using amplified nucleic acids that are less than 100 bp long as suggested by Monforte because current mass spectrometric methods do not have the mass accuracy and resolution necessary to identify single base changes in polynucleotides larger than 100 base pairs.

Regarding Claims 23-24 Olek et al do not teach a method wherein (i) the methyl group carries a label which is incorporated into the synthesized nucleic acid strand and (ii) a mass label that is incorporated into the amplificate nucleic acids.

However Monforte et al teach a method wherein the amplified target nucleic acids have one or more nucleotides replaced with mass-modified nucleotides, wherein said mass-modified nucleotides comprise nucleotides or nucleotide analogs having modifications that change their mass relative to the nucleotides that they replace. The mass-modified nucleotides can be incorporated into the target nucleic acids during amplification. Additionally the replacement of a methyl group by heptynyl changes the mass of this particular nucleotide by 65 Da (Column 22-23).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Olek et al by using mass modified nucleotides as suggested by Monforte because mass modification can generally increase the quality of the mass spectra by enlarging the mass differences between different amplified target nucleic acids of similar size and composition.

7. Claim 21 is rejected under 35 U.S.C. 103(a) as being obvious over Olek (US Patent 6214556 Issued 2001) in view of Olek (US Patent 6977146 Filed July 2001).

The teachings of Olek et al are presented above in paragraph 4.

Regarding Claim 21 Olek et al does not teach a method wherein the detection step comprises comparing the obtained mass spectra with a reference mass spectra and determining the methylation pattern.

However, Olek et al teach a method wherein the detection the characteristic methylation patterns of the investigated DNA sample is the peak pattern produced by

the probe in the mass spectrometer. Then these methylation patterns are compared with those of a database (Column 7).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Olek et al by comparing the obtained mass spectra with a reference mass spectra as suggested by Olek because the method of Olek is an equally effect means for analyzing a nucleic acid fragment for methylation.

8. Claim 22 is rejected under 35 U.S.C. 103(a) as being obvious over Olek (US Patent 6214556 Issued 2001) in view of Van Ness (US Patent 6884586 Filed July 2002).

The teachings of Olek et al are presented above in paragraph 4.

Regarding Claim 22 Olek et al does not teach a method wherein the detection step comprises determining the molecular weight of the fragment and then determining the methylation status of said fragments.

However Van Ness teach a method in which the molecular weight of an amplified single-stranded fragment determined by mass spectrometric analysis may be compared with the predicted molecular weights of two single-stranded fragments, respectively: one fragment amplified using a portion of a target nucleic acid where the nucleotide of which methylation state is of interest is assumed to remain the same after the treatment of a modifying agent, the other amplified using the portion of the target nucleic acid where the nucleotide of which methylation state is of interest is assumed to be converted to

another nucleotide by the treatment of the modifying agent. The above comparison may indicate whether the nucleotide of which the methylation state is of interest has, or has not, been modified by the modifying agent. Based on the above indication, one may determine the methylation state of the nucleotide of interest in the target nucleic acid (Column 28).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Olek et al by detecting the molecular weight of the fragments as suggested by Van Ness because the method of Van Ness is an equally effect means for analyzing a nucleic acid fragment for methylation.

9. Claim 26 is rejected under 35 U.S.C. 103(a) as being obvious over Olek (US Patent 6214556 Issued 2001) in view of Koster (US Patent 5547835 Issued 1996).

The teachings of Olek et al are presented above in paragraph 4.

Olek et al teach a kit for the detection of a methylated CpG-containing nucleic acid, wherein the kit comprising reagents for the methylation retaining amplification of genomic DNA (Column 10)

Olek et al does not teach a kit comprising reagents for the mass spectrometric analysis of nucleic acids.

However Koster et al teach kits for DNA sequencing by mass spectrometry (Column 20).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the kit of Olek by additionally including reagents for the mass spectrometric analysis because reagent kits for performing mass spectrometric assays were conventional in the field of molecular biology at the time the invention was made. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the reagents for amplification and reagents for mass spectrometric analysis in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to analyze methylation patterns via mass spectrometry.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of

copending Application No. 10509144 in view of Olek. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are coextensive in scope. As defined by the '370 application, the claims of the '144 application are carried out by amplifying a nucleic acid and subjecting the amplfiicate to a treatment which maintains the methylation pattern of the template strand in the newly synthesized strand. The instantly filed claims are also drawn to a method comprising amplifying a nucleic acid sample in a manner in which the methylation patterns are maintained. While the claims of the '370 application do not teach the detection of the amplificate using mass spectrometry, Olek teaches the detection of methylation patterns using MALDI-TOF. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of the '144 claims to include analysis with MALDI-TOF because Olek teaches an effective method of detection of methylated and unmethylated cytosine using such.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 1-26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-35 of copending Application No. 10/363,345 in view of Olek. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are coextensive in scope. As defined by the '345 application, the claims of the '345 application are carried out by subjecting a sample to bisulfite treatment, amplifying the

target nucleic acid and performing hybridization in order to determine the methylation status of the sample. The instantly filed claims are also drawn to a method comprising amplifying a nucleic acid sample in a manner in which the methylation patterns are maintained (i.e. by treating the sample with treating the sample with bisulfite) and determining the methylation status of the sample. While the claims of the '345 application do not teach detection using MALDI-TOF, Olek teaches the detection of methylation patterns using MALDI-TOF. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of the '345 claims to include analysis with MALDI-TOF because Olek I teaches an effective method of detection of methylated and unmethylated cytosine using such.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 1-26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-43 of copending Application No. 10/057776 in view of Olek. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are coextensive in scope. As defined by the '776 application the claims of the '776 application are carried out by application are carried out by subjecting a sample to bisulfite treatment, amplifying the target nucleic acid and detecting a fluorescent label in order to determine the methylation status of the sample. The instantly filed claims are

also drawn to a method comprising amplifying a nucleic acid sample in a manner in which the methylation patterns are maintained (i.e. by treating the sample with treating the sample with bisulfite) and determining the methylation status of the sample. While the claims of the '776 application do not teach detection using MALDI-TOF, Olek teaches the detection of methylation patterns using MALDI-TOF. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of the '776 claims to include analysis with MALDI-TOF because Olek teaches an effective method of detection of methylated and unmethylated cytosine using such.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

14. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER